DRUG-INDUCED SCHIZOPHRENIA*

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INTRODUCTION

MEDICAL research is simpler and generally more productive when it becomes possible to use models. This experimental method is available to psychiatrists who find that certain chemicals called hallucinogens (13) produce in subjects experiences which resemble those described by patients who now have schizophrenia or by those who have recovered. Lewin (19), Kluver (18) and Stockings (31) suggested many years ago that these compounds could be used in this way. However, the differences between these model experiences and schizophrenia rather than their similarities impressed many leading psychiatrists. Thus Bleuler (4) as late as 1956 maintained that lysergic acid diethylamide (LSD-25) produced a toxic delirium and therefore this experience had little to offer to the students of schizophrenia. The fallacy of this argument was discussed by Osmond (23) who with Smythies (24) stressed many points of similarity between schizophrenia and the mescaline experience. The consensus today of research psychiatrists such as Rinkel (26, 27, 28, 29), Hoch (10, 11) and others is that the similarities are adequate, provided generalizations remain within the limits imposed by the data.

LSD produces an experience for many subjects which closely models schizophrenia. There are, however, many differences due to variables such as the presence of insight (the subject has an adequate explanation for the experience being present), the setting, the rapidity of onset, anxiety and the objective. Most schizophrenic patients develop their disease slowly and if they recognize that they are being altered have no adequate explanation. In any event, this alteration leads to an increase in anxiety. When the illness is well advanced anxiety appears to be damped, inappropriate or flat. In fact, some clinicians hesitate to diagnose schizophrenia until this affective deficiency is clearly present. The psychotomimetic drugs, on the contrary, mobilize and deepen the intensity of emotion. The subject may have fear and terror or the euphoria of the transcendental experience, but the affect is rarely flat. In our studies of well over three hundred LSD experiences, we have not seen this. Indeed this intensification of emotion is probably of great therapeutic value in the treatment of psychopathic and alcoholic patients, Smith (30), Chwelos, Blewett, Hoffer and Smith (7).

The reproduction of a model of schizophrenia where a flattening of affect

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is predominant is therefore interesting and may perhaps be useful. This has occurred recently in one of our LSD trials in a normal volunteer and is the subject of this report.

Substances which antagonize the LSD experience are theoretically important, as they may lead to better treatments for schizophrenia. Nicotinic acid, for example, which modifies the experience also cures many early schizophrenic patients when given alone or in combination with E.C.T. (14). Penicillamine is a possible treatment for schizophrenia because *in vitro* this sulfhydril compound converts adrenochrome predominantly into 5, 6-dihydroxy-*N*-methylindole. The latter is not psychotomimetic (12) whereas the former is (13). Since the psychological activity of LSD-25 is closely correlated with increased levels of adrenochrome in the plasma, it seemed possible that if penicillamine were given with the LSD-25 the experience might be modified because the adrenochrome level would not rise—as it usually does.

Previous Experiences With LSD-25

The subject had received LSD-25 twice previously under our direction. A partial account of these experiences written by her shortly after follows.

First Experience. The purpose of this experiment was to discover how certain nursing techniques affect someone who has taken LSD-25.

About 15 minutes after the ingestion of LSD-25 (100 μg.) I became hyperacute to vibration. When the bed was touched very lightly without sound or without my seeing this movement, it felt to me as though the bed were being pushed or kicked. In addition, I felt as though there was pressure behind my eyes and they felt heavy. I had a tingling sensation in my tongue and hands. Within the next ten minutes, I noted a shimmering effect in the room and then patterns starting to form on the walls. When attempting to read, the lines tended to roll upwards toward the top of the page. Forty minutes after taking LSD-25, on looking at my left hand it seemed to shrink and wither. On looking at my feet, they seemed very narrow but as I brought them closer they became very broad and large.

During this period, I experienced some anxiety, irritability and slight euphoria. Some nausea of a butterfly type was noted but it did not remain very long.

During the next two hours, I was subjected to a variety of nursing approaches. When I felt comfortable with the nurse, the room seemed very bright and at times there seemed to be a lovely orange halo around the nurse's head. When I felt rejected and threatened, the room would appear cell-like with very drab colours. On one occasion the nurse assumed the appearance of an animal, then on looking away from her and at my knees, I too seemed to turn into another animal with whiskers growing out of my mouth. This terrified me and I seemed to be wandering around lost in a long tunnel through which the wind was howling. I felt this lasted an eternity when in reality (according to the tape recording) it lasted under a minute. My mood changed quickly but was appropriate to the situation as I experienced it.

The lighting in the room was changing constantly as well as the dimensions. My perception of depth shifted fluidly. Flat surfaces often changed so that I saw what looked like the basic structure of the material. At times a fly which was actually in the room would become a swarm of them in flight. This occurred in the third hour and eventually I came to realize there must be a fly present because a single one would light on an object but none of the others ever did.

My concept of time was disturbed; the day seemed to cover years. My thinking was very concrete and quite paranoid at times. Blocking was apparent during the height of the experience. I was disoriented as to place and person on only one occasion as mentioned above. My emotions were highly responsive. I communicated very little verbally with the observers present—perhaps for two reasons, (1) things changed too rapidly to give a coherent account, and (2) the unpleasant nature of much of the experience.

During the fifth hour the experience receded in waves. It was suggested that I take nicotinic acid 1 gm. by mouth to terminate it more quickly but I refused. I had a tingling sensation over my body and felt the effects of the nicotinic acid would heighten this even more. I was still slightly paranoid on occasion and my mood tended toward mild depression.

From the fifth to the ninth hour I was very quiet and introspective. I was at a friend's home for supper (still under observation) and found it hard to converse with those present. Food was tasteless to me and I was still aware of the "whiskers" in my mouth. I was extremely tired as well. After supper we were listening to a radio commentator, but I was unable to concentrate enough to understand the content. My cigarette tasted odd to me, so at this time I asked to be given nicotinic acid. About 15 minutes after this I became quite alert and felt

normal again. I could follow conversation easily and could now relate my experience to the others.

That night I took Tuinal 400 mg. and slept very well. I awakened in the morning feeling quite refreshed, cheerful and alert. At work that day I began to dictate my recollections of the previous day.

This experience took place four and one half years ago and still remains very vivid in her memory although she referred to her notes for this report.

Second Experience. The subject took LSD-25 to enlarge her understanding of the psychedelic reaction.

About twenty minutes after the ingestion of LSD-25 (100 μg.) I began to feel slight changes. There was a tingling sensation in my tongue, arm and leg. One half hour after the start of the experience I noted changes in lighting and a shimmering effect in the room.

During this period, music was playing which I found interesting and enjoyable. I felt no anxiety and was quite relaxed, no nausea was present.

Fifty minutes after I took LSD-25, my right hand appeared to change in size and texture. When I looked at reproductions of oil paintings—flowers seemed to be sculptured in clear harsh surfaces. I could see no beauty or life in them. The lighting effect in the room was heightened but there was very little disturbance of depth perception. My mood remained pleasant and I found the experience interesting.

About one and one half hours after the start, I was really into the experience and it remained intense for the next two hours. I was asked to look into a mirror and I saw my image change gradually to that of an older and older "me", until eventually I seemed to get right into the mirror and look out from there. When I looked at paintings of people, they got older, then younger. Occasionally I was completely engulfed in the portrait. I found the paintings fascinating, and landscapes as well were beautiful beyond description, very much alive, and produced a tremendous amount of emotion in me.

When I looked at the people in the room with me, changes occurred in them. One person's face became older, then changed into an Egyptian—later a mosaic pattern formed over his entire face except for one cheek which bore a shield. Sometimes a further change occurred and he resembled a Zulu warrior.

I was able to travel back in time and saw myself at different ages in my family setting and was quite surprised by some events I saw taking place.

I travelled in space to various parts of the world, to other planets and to the bottom of the sea. I found this most interesting and enjoyable. I was tremendously impressed by the comprehensiveness of the universe and the insignificance of the human being with his petty problems.

During these two hours, time had no meaning for me—I was bound by neither time nor space.

Parts of a tape recording of the chanting and drumming by Indians of the Native American Church of Canada performing a peyote ceremony were played for me during the fourth to fifth hour. While I listened, symbolic pictures formed (it made no difference if my eyes were open or closed) by which I felt I could interpret the messages of the drums and the prayers. My emotions corresponded to my interpretation and I was tremendously moved by the whole ceremony.

Time was unimportant to me. I seemed to live a lifetime in seconds. My thinking was very clear. I was never disoriented as to place or person. At no time did I lose sight of the fact that I had taken a drug which had induced this "amazing" experience. I was able to communicate freely to those present what I saw and felt

During the fifth hour the experience receded in waves. I was somewhat introspective, but at the same time could readily relate to those around me. I felt bathed in a warm glow. I was tired but happy. Music was playing most of the time and I was very responsive to it.

I went to a friend's house for supper and enjoyed the company. I ate only a small meal because I was not really hungry. I told my friends about the experience and we were all very gay.

When I went to bed I took Tuinal 400 mg. and soon fell asleep. In the morning I felt quite refreshed, alert and still retained this feeling of well-being. I had no difficulty carrying out my usual assignments at work during the day.

The subject recalls this reaction essentially as a "feeling experience". The transcendental qualities had a sustained effect upon her.

The Experiment

The subject was a female nurse, age 35, who had received 100 micrograms LSD-25 in September, 1954 and again in January, 1958. She had also partici-

pated in many LSD treatment sessions with patients as well as assisting in experiments with volunteers. She was skilful in introspection as well as in verbalization. She was confident in the senior author's opinion that penicillamine given in advance would prevent any LSD-25 experience.

For two days before the LSD-25 experiment, she ingested 2 grams of penicillamine in capsules containing 0·5 grams, in four doses. On Saturday, the first day, she was nauseated after the second dose and thereafter after each dose. During the afternoon she felt lethargic and slept. On Sunday, the second day, she was very disturbed by the powerful odour of the penicillamine which appeared to diffuse from her skin. She remained lethargic and did not sleep well at night. Monday morning, she took a further 0·5 gram capsule at 7.15 a.m. At 9.15 a.m. she was given 100 μg. LSD-25 by mouth.

Report by Observers

9.15 a.m. She reports the penicillamine odour is making her feel sick.

9.45. She feels some tingling of her hands as well as some numbness. The typical (for her) LSD-25 sensation of something behind her eyes is present.

10.00. The room seems much brighter; objects stand out in sharp detail. Some nausea is present and she is very restless and bothered by the odour.

10.07. She continues to be disturbed by the odour but wonders if she is hypersensitive to it. She now feels cold. Her pupils are not dilated.

10.15. The lights seem dazzling bright. With her eyes closed she can visualize symbols related to the stench. She laughed briefly and appears slightly happier.

10.25. She reports some distortion of depth perception. The walls are either too far or too close. She is very tense and has a marked tremor. She states the experience is horrible but it does not frighten her.

10.40. The subject feels drunk. Mild visual changes are present and she has difficulty in concentrating. Her sensation of taste is gone. Pupil size is 1/4 (pupil diameter one-quarter of corneal diameter).

10.50. Visual changes are very pronounced. Her mood is neutral, then she was able momentarily to enjoy music. Later she visualized a very gruesome-looking object which did not frighten her. Pupil size 1/3.

10.55. Visual distortions are present but not interesting; she is quite indifferent to the visual phenomena.

11.05. She reports she cannot feel emotion. She hears the music, observes the visual changes, smells the penicillamine, but is completely disinterested. When she was asked if she would take more penicillamine replied "I don't care".

11.25. Marked visual changes are present but they are not interesting. The inner tremor is still there. So far the subject has not had any sense of relaxation or pleasure.

11.40. She is visually very alert and can clearly see specks of dust jumping up and down on the revolving record. In reply to a question she denies feeling sleepy. She is not mentally alert, nor tired. Some nausea is present. Now and then she is unaware of her body. Pupils are 1/3.

12.00 noon. She is still unaware of her body but not relaxed. For a moment she felt she was coming out of her experience. She is completely indifferent to music. In response to a query she replied she "could not care less".

12.20. She reports she is definitely coming out of her experience as the

visual imagery is changing less rapidly. The penicillamine odour bothers her once again.

12.35. She feels somewhat more normal and more aware of her body but does not care. She reports she can hear the music but is not interested. Her visual memory is gone. Normally she can visualize people whenever she thinks about them.

12.50. She sees animals in the folds of some window drapery (none are there). The patterns are striking and resemble needle point.

1.05. Visual changes are less noticeable. The room is now stable. Pupils are 1/3.

1.27. She was given one gram nicotinic acid by mouth in order to bring her experience more quickly to an end.

1.42. Visual changes are less noticeable. She is now able to talk more freely. The flush (from the nicotinic acid) starts. She reports little feeling is present.

1.47. She still sees bears and horses in the drapery. She reports some feeling is present. Her visual memory has not returned.

1.54. She is quite flushed. When queried about degree of feeling she was unable to know because of the flushing and burning feeling.

2.05. Visually objects are quiet but still stand out in sharp relief. She reports that the nicotinic acid has helped her.

2.17. Slight visual changes still present. She feels no better but appears more alert.

2.23. She was momentarily uncertain whether she had had any experience. Now she reports some slight appreciation of music.

2.32. Subject complains she is cold. The visual changes are nearly gone. She was given 1 gram ascorbic acid by mouth. She thought it was more nicotinic acid but did not care.

2.52. She had lunch consisting of an egg sandwich and a cup of coffee. The egg tasted like egg only on the third mouthful.

3.04. Subject shivered and still feels cold.

3.24. As above.

3.40. The flush due to nicotinic acid is still present but she is cold. Pupils are 1/3. Her fingers are cyanosed.

4.20. Subject still is flushed and cold. She remains without any feeling, being neither depressed nor happy.

4.45. Her legs are now flushed and she is less chilly.

5.10. She is able to think more clearly and to follow conversation. Vision is normal. She appears more normal than at any time during the experience.

6.00. She ate soup and toast at a friend's home. There was no emotional reaction. At her own home she was given 400 mg. Tuinal. She noted she was not able to close her eyes.

7.00. As she was not asleep or sleepy she was given 200 mg. Tuinal. Finally after two cocktails she fell asleep while watching television at 9.30. Once during this period she felt she would never again be able to feel but this did not depress her.

Report by Subject

The following account was written six weeks after the experiment.

I took penicillamine Saturday and Sunday as ordered and with the effects as reported. When I came to the office to take LSD-25, I felt rather sick, due to the clinging odour and some nausea. I expected nothing much would happen during the experience. I was not tense, I just wanted to get the experience over with so I could be finished with the penicillamine.

I took the LSD-25 at 9.15 a.m. During the next hour I had a fleeting feeling of tingling in my hands and the typical LSD-25 feeling behind my eyes. Also there were moments when detail stood out more clearly but these were not sustained. I was terribly aware of the odour and felt nauseated. This feeling compared with the nausea I experienced over the weekend and was not like the fluttery feeling usual for me after LSD-25. Toward the end of the hour I became restless and more sickened by the horrible odour. During the second hour I began feeling quite cold and I think I remained cold until about noon. When I closed my eyes I envisioned mounds of ulcerative decaying flesh. I felt it strange that this imagery should not be repulsive to me or frighten me—I merely noted and reported it. This imagery came in waves for a short time and seemed to me to relate to the odour. Following this, I noted very slight visual changes, mainly in lighting and depth perception within the room. Music was playing and I was aware of it but not responsive to it. I remember remarking that when some Mexican music was playing I would expect to imagine fat paunchy little people but this was not the case now. It became a bit difficult for me to think clearly, but there was no overall time distortion. About one and a half hours after I took LSD-25, I began having marked visual distortions which I associated with former experiences. The striking differences were that (1) they were not preceded by the usual shimmering effect, (2) they were clear-cut distortions of pattern and depth rather than an effect superimposed on a surface, (3) the distortions did not take the form of human beings and that (4) they elicited no emotional response from me. As these changes became more marked, I became unaware of the odour and of my body. During the next hour this visual flow was very striking and fast moving. Music was played throughout and I was quite aware of it but not involved in it in any way. When I looked at the record player I was very sensitive to the sight of the record turning around and the spots of dust jumping up and down. I was asked to try to leave my body but this I could not do. I was entirely unaware of my body, I could neither feel nor imagine, so (to me) actually there was no "me"; I did not exist. During this time the experience consisted of one area where visual changes were occurring and one area where music was being played. There was no relation one to the other and I was merely an instrument noting these facts like a camera making an impression on a negative.

Shortly after noon I could make out an animal from a distortion of the drapes so I commented on this, saying I was coming out of it. Soon after this I could make out two people leading a horse and for the first time I had a fleeting surge of feeling (interest) and thought my emotions would return. I said I was definitely coming out of the experience and waited for a flood of emotions. The visual flow slowed down. I became aware of my body and aware that I was now warm. (I had wrapped myself in a blanket in a most uncomfortable position, so I now removed it and made myself comfortable.) During the next half hour the two areas became three areas—i.e. visual, sound and body—but there was no harmony between them and each existed as a separate entity. One of the visual effects that was most marked now was a distinct stroboscopic effect of movement. I had never seen it to this degree before. I commented upon it as a neutral observer would. Also there was marked after image seen peripherally.

Between 1 p.m. and 2 p.m. I became aware, once more, of the unpleasant odour but it did not overpower me as earlier. I noticed it mainly when I voided. The visual flow subsided but detail stood out very clearly still. I was given 1 gm. of nicotinic acid by mouth which I took automatically—I had protested vehemently on previous occasions when I had had LSD-25. The flush that followed was not unpleasant. In fact, I was unaware of it unless my attention was drawn to it. It lasted an unusually long time and I remember when I got ready for bed at about 6 p.m. I noted my body was still flushed. (My normal flush from nicotinic acid lasts about one hour.) During this period I knew my emotional tone had not returned. I tried to visualize the faces of my friends, as I normally can when I think of them, and have always been able to do in previous LSD-25 experiences, but was totally unable to do this.

Following this, I began to have a feeling of uncertainty as to whether or not I had been the one who had the experience. The visual changes had lessened considerably, but I was still without feeling. This did not worry me at all, I merely reported it as unusual. It became necessary for me to produce another specimen of urine for the laboratory but I was unable to do this, and this too I found strange. I was given a cup of coffee which tasted like coffee and an egg sandwich which I could identify as egg but otherwise was not tasty. I consumed this lunch automatically. I still found it hard to comprehend conversation directed toward me, but followed short orders like an automat. I began to feel chilly again and this continued until I went to sleep that night. At no time did I recognize myself as feeling tired, which is quite unusual for me following a long LSD-25 experience.

I was taken to a friend's home for supper—part of which I consumed. While there, I could correctly identify the feelings of those around me, but was not able to respond to them. I felt confused by so many people and so much activity, so I quickly gave up eating and asked to be taken home.

I was given 400 mg. Tuinal at 6 p.m. and went to bed but was unable to keep my eyes closed and go to sleep. About 7 p.m., I believe, I was given 200 mg. more of Tuinal. Until I went to sleep about 9.30 p.m. or so, I had in addition two cocktails of rum and coke. I remember expressing the idea that since I was unable to "feel" I would never be able to sleep again either. I was out of bed and walking around twice that I know of between 9.30 p.m. and 1.0 a.m.—that it, I wakened up and walked around a bit, sat in the living room and watched

T.V. for a short while. I slept soundly from 1.0 a.m. to 9.0 a.m. the next morning. At that time I walked around a bit again, then returned to bed and slept until noon.

AFTERMATH

1st Phase—Tuesday to Friday inclusive (Days 1 to 4)

Two months after the experiment the subject wrote as follows:

I call this the stage of "automatic behaviour". I came to work automatically, ate at the proper time, pin-curled my hair in the evenings and went to bed at the appropriate time, etc. In the morning at work I would do routine things as soon as I arrived, but during the rest of the day I just sat at my desk doing nothing. If anyone gave me a simple task I could do it, but when that was finished I would resume my sitting. I was quite aware of the people around me and could identify their feelings but did not respond to these feelings. (My co-workers were either frightened, worried, or felt sorry for me. In general, they felt uncomfortable in my presence.) I had no initiative or interest in anything. I had difficulty in following conversation and realized my thinking was not normal and that my judgment was impaired. This did not worry me but being aware of it I checked and rechecked the few things I did to be sure they were correct. I could relate superficially to one person and even to two people if I could watch them closely. In order not to appear too strange to people, I used my past experiences as clues or guides to outward appropriate behaviour. If more than two people were present, this broke down. I became confused, gave up all pretence of being a social animal and retreated within myself.

In the evenings I watched TV continuously—no matter what programme was being shown. Usually I could not follow the content very well and at no time did any programme have an emotional impact on me. The only time I turned the radio on was to listen to news broadcasts and then would turn it off immediately. Some of the news items stuck with me—others did not even register. My pattern of reading was entirely changed. Usually I read two to three books (novels) a week and although I had some new ones at home I never picked them up. Instead I read the newspapers more thoroughly than I ever did before in my life. Even an out of town newspaper which I take kept me active for hours reading all the classified ads. I remember one night when I never slept at all sitting up in bed from about 2.0 to 5.0 a.m. reading the one paper.

Physically, the major thing I noticed was the progressive dryness of my mucous membranes and skin. During this period the main discomfort from this was the fact that I could not keep my "gritty" eyes closed. My lids would fall naturally about half-way down but beyond that I had to force them and they tended to fly up again. I found it quite strange to attempt to fall asleep with my eyes partly open and this may have had some effect on my sleep pattern. The other thing I noticed was that I frequently felt chilly.

Verbal communication was full of pitfalls. I never realized before that the English language is full of "loaded" words, that is, so many words have an emotional value. I was unable to use these words and as a result my conversation was very stilted and what I would call formal. I could use none of the ordinary social amenities—no please, thank you, or hello, etc. On one occasion, one of my colleagues gave me an unusual box of matches. I felt I could not keep it because he would then expect at least a thank you. I did not know what to do, when suddenly I heard myself saying: "I don't require matches. I have a lighter." When I say I heard myself, it was exactly that. I did not plan in advance what to say on these occasions and it sounded like a tape playing back my voice. I quite recognized my style of speech was strange for me and noted it as unusual but otherwise was not concerned about the situation.

During this entire period, I recognized the fact that I was devoid of feeling, my thinking was impoverished and somewhat confused, my judgment was impaired and that I had never been in this state before. I believed it had come about because I had taken this particular combination of drugs. However, I believed this to be irreversible and was not in the least concerned about it. From time to time Dr. H. would explain to me what he felt had happened and predict the course it might take. I would either agree or disagree with him, but it was as if we were discussing a patient, not myself.

The following notes were made by the observers on the days indicated.

First Day. The subject awakened at 9.30 a.m. but slept again until 1.00 p.m. She then came to work at 3.00. Her face was very pale and her pupils were pinpoint (less than 1/4). She reported that she was able to think clearly but did not know whether or not feeling was present. Slight visual changes remained. She still saw the drapery stand out very sharply in relief. She remained without feeling all day.

Second Day. Although she felt somewhat better than the previous day, little emotion was present. In the evening she said she would be sad if she could

feel but there was no real sadness in her. She consumed three cocktails at home but noted no effect and then took 100 mg. seconal at 11.30 p.m.

Third Day. She awakened at 7.18 a.m. and then slept again until 9.00 a.m. No feeling was present. She came to work but could not accomplish anything. To the senior author she appeared to be in a serious psychotic depression. However, she denied being depressed. Her reaction seemed so similar to a reserpine-induced depression that she was given 10 mg. dexedrine by mouth at 1.30 p.m. In one half hour speech was more spontaneous. At 2.08, the tension so apparent in her face began to lift. At 2.20, all her face felt normal except for a band-like area encircling her head. Her face regained some colour. At 2.30, she reported a momentary feeling of interest in life. At 5.00, she drove home in her car and at 6.00 had dinner with friends. Before dinner she took a 15 mg. dexedrine spansule. The experience during dinner was dreadful because she had no feeling and was not able to engage in conversation with other members of the dinner group. At 7.30, the inner tremor she had felt the day she had received LSD-25 returned and she was very chilly for nearly one hour. Suddenly she felt reasonably good and was able to talk more freely. However she remained cold all evening. She took 100 mg. sodium seconal at 12.00 midnight, but did not sleep. At 3.15 a.m. she took another 100 mg.; at 4.00, she developed an odd feeling which she decided one half hour later was hunger. She then ate a substantial lunch. Following this, she took a prolonged hot bath, ate some more and went to work at 9.35 a.m.

Fourth Day. She reported she had some feeling this morning, could talk fairly well and was able to relate to people more appropriately but felt very formal with them. She expressed some optimism that she might eventually be normal. The drapes had lost their tapestry-like appearance and appeared normal. She had vague momentary feelings of well-being. A laboratory test she had ordered was ruined. There was no reaction from her whereas normally she would have been very much annoyed and irritated by this.

She remained this way until noon when she drove home for lunch. She had no appetite and did not enjoy eating. The news on the radio had no meaning for her and driving back to work she could not remember what had been said. After lunch she felt she was better than yesterday because she was able to experience some tension now and then. Toward mid-afternoon she became more and more withdrawn until she reached her lowest point at 3.00. She was now very cold and was given 10 mg. dexedrine. At 5.00 p.m. she was able to talk better. There was no change the rest of the day.

2nd Phase—Saturday to Thursday (Day 5 to 10)

The subject called this phase the stage of suspended animation.

Fifth Day. Saturday morning about 11 a.m., I began to feel extremely cold. I had the thermostat set at 80°, was in bed wearing a flannelette nightgown and had a heating pad turned on high. As time went on I got colder and colder. The sun was shining brilliantly through the venetian blinds and I was lying on my side with my eyes open facing the sun (usually I lie on the other side). I don't know how long I remained there motionless, but it was at least two hours and probably closer to four hours. I believed I would die and judged myself to be about three-quarters dead at that time. I was not at all disturbed by this—merely waited for the last quarter to go. I was given medication and eventually warmed up.

She was seen on the fifth day at home. She was very cold, cyanosed and her hands were cold to touch. Her pupils were pin-point. Pulse was 60.

No feeling was present. She took 5 mg. methedrine about 3.30 p.m. and read for awhile. About 3.50 she suddenly became very warm with a prickly

sensation in her skin similar to a mild nicotinic acid flush. She became more comfortable and had a twilight sleep with hypnagogic phenomena. One half hour later she was awakened by one hand falling asleep. She still was comfortable and felt relaxed with her eyes closed until 5.00 p.m. She felt warm. Pupils were pin-point. This was the first time she had been able to keep her eyes normally closed while awake and resting. She felt she had some positive feelings. Her skin was very dry. At 6.00 p.m. she became chilly and took 10 mg. methedrine. At 6.40 she was really hot; at 7.55 her hands were wet (first perspiration all week). At 9.00 she was still warm and her hands moist. She watched television all evening but with no interest. It was something to do. The programmes were dull. She was able to follow the story, but when watching hockey could not remember which side was winning. At 11.30 p.m. there was no further change. Pupils were 1/8. She washed her face and watered the plants. At 12.45, she took 400 mg. Tuinal and a cocktail and slept by 1.45 a.m.

Sixth Day. She slept well and awakened by 11.15 a.m. She was warm, pupils were 1/4 to 1/3. She felt alive and alert but now noted some trace of penicillamine odour. At 12.45 she ate a lunch of tea and toast and then noted she had less of the alive and well-being feeling. Although she was regressing she remained warm and her palms were moist. Her eyes were tired. At 1.40 p.m. she took 5 mg. methedrine. At 2.35 she was very hot and felt as if she was perspiring and itchy but there was no perspiration. The hot feeling was present momentarily. At 3.45 she was invited out for dinner but was very uncertain how she would react to people. Pulse 78. At 4.35 she noted she was getting colder and took 5 mg. methedrine. She felt weak and shaky for two hours as though this was the first day up after being confined to bed for several days. Pulse 70. At 5.15, her hands were warm but her feet were cold. She did not feel alive but felt better than yesterday. 8.30—During dinner she was able to talk fairly well at first but this became more difficult later on. About 7.15 became cold which was marked by 8.30. Her right eye ached severely. Pupils were pin point. No feeling was present. She took 10 mg. methedrine. At 9.10 she was warmer but her hands were cold. At 10.30 she was hot, her eyes were normal. Pulse was 90. 10.40—400 mg. Tuinal and slept until 4.00 a.m. She was extremely restless so took Tuinal 200 mg. and slept until 11.00.

Following this experience, during this second phase, the outstanding thing was this awful cold. When I felt myself starting to become cold, I became mobilized to do something to prevent it. This was much more important to me than the loss of feeling tone. The automatic quality of my behaviour disappeared to a large extent. I did not go to work unless I was told to. I no longer pincurled my hair. I did eat fairly appropriately, because I felt this might prevent my getting cold. My thinking was still confused and became even more concrete. My judgment was more impaired and I felt very uncertain of my ability to comprehend and remember. I made copious notes related to medication and its effects on me. I felt it necessary to have definite directions written regarding medication. I asked for guidance continually as to what I should do and when.

My mucous membranes became so dry as to cause actual physical discomfort. My nose bothered me terribly and my eyes ached. Food had no taste and at times it was difficult to force it down, my mouth was so dry. I drank large quantities of fluid.

Towards the end of this time, when I was warm I would think that perhaps I might be able to feel again sometime in the future, but when I was cold I would again think this was irreversible. However, the cold spells became more infrequent which in turn fostered the belief that I would become normal. The last day of this phase I remember remarking to someone that if I ever smiled again I felt my face would crack, it felt so set and rigid. That night my jaws started aching noticeably and this lasted all evening.

Following are some further excerpts from the subject's notes made during this phase.

Seventh Day. 3.25 p.m. Pupils 1/4 to 1/3. Have been reading articles in a magazine without interest but am able to follow it quite well. Have not experienced that very cold feeling of Saturday or the chill of last night. Pulse 80. Find it hard to compare my state to any day but Saturday. Emotion or its lack does not seem important rather the physiological condition. Saturday was the worst day because of the physical coldness with the absence of any feeling. This was like a dead feeling. I have not recognized any tension since Friday.

6.0 p.m. Ascorbic acid 1 gm. I am having a sensation which I can only call one of anticipation, as though my system was ready for an emergency. I do not know whether to take methedrine. It is practically impossible to judge after all these days, as long as my body is comfortable; when the freezing cold is present I know. I am now warm except for my feet. Surely it won't hurt if I wait until 7.0 p.m. to take methedrine.

7.0 p.m. Have had 1½ drinks of rye and feel inebriated—unusual for me except maybe my nutrition is not what it should be. Eating a hotdog. Feel neither depressed nor happy. Have not any judgment about taking methedrine so will not take any.

10.30 p.m. Confused about instructions doctor left me. Tuinal 200 mg.

11.0 p.m. My reasoning seems to be off. Last night I needed 600 mg. Tuinal so why do I think 200 mg. will do now? This is the first day which has seemed so long. It has not been boring. Will set my alarm for 8.30 a.m. and if I feel well will be at work by 10.30.

Eighth Day. 2.35 p.m. Hands cold for some time now. Not as good this afternoon. Either the room or I am getting cold.

3.20 p.m. Ten mg. methedrine.

4.0 p.m. Rushed home—very cold and stated if I do not get home now may not make it.

Ninth Day. 3.30 p.m. Propane gas people were changing tanks next door causing quite a commotion. I became quite apprehensive and although I felt sure that was what was going on, I got up and looked out. I don't think I would have done this a couple of days ago.

10.0 p.m. Feel a desire to communicate with people. Would phone R. but am afraid I wouldn't have anything to say.

The observers noted the following:

Tenth Day. 10.30 a.m. Coffee. Started to feel cold. Methedrine 10 mg. Pupils pin-point.

10.50. Two inhalations med-adrenaline (200 μg.)*.

11.00. No effect. Two more inhalations.

11.05. Faint flush on face visible. Slight feeling of warmth. Warming up.

11.14. Getting chilly again.

11.25. Chilly, shivery.

11.28. Pulse 70. Pupils pin-point.

11.30. Warming up.

11.34. Still warmer. Pulse 74. Pupils 1/4.

12.00 noon. Warm inside.

12.40 p.m. Have been sneezing and blowing my nose ever since arriving home. Have a sensation of something bothering my nostril. Can't stop sneezing long enough to make lunch.

12.50 p.m. Not sneezing now but still blowing an amazing quantity. Sensation still there but not as marked.

1.05 p.m. Eating lunch but still blowing just as if I had a very bad head cold which I haven't. Feel warm.

1.25 p.m. Still blowing and sneezing. Pupils 1/4. Pulse 76.

2.0 p.m. Starting to feel chilly. Still sneezing and blowing. Maybe a cold is starting.

2.03 p.m. Two inhalations of adrenaline. An immediate reaction, heart pounding. Pulse 78. Pupils 1/4.

2.08 p.m. Pulse 82. Still shaky but not so badly. Heart still pounding. Pupils unchanged.

2.13 p.m. Pulse 80. Body feels warm but hands are cold.

2.15 p.m. No more sneezing although blowing nose occasionally. Chest feels a bit tight.

2.25 p.m. Pulse 80.

2.50 p.m. Blowing nose almost continually. Feel warm. Pupils 1/4.

3.0 p.m. Real warm but not perspiring. Pupils 1/4. Ten mg. methedrine (as ordered).

4.30 p.m. Pulse 76. Warm. Have not blown my nose for ten minutes. Longest period of time.

6.0 p.m. Sneezing again and more nasal discharge. Ten mg. methedrine. My eyes have been bothering me as though I were stuffed up with a cold for some time now.

6.30 p.m. Pupils 1/6. Really believe I have a cold. Sneezing, coughing and blowing. If this was a cold, I would be perspiring but am not. Jaws are aching.

* Medihaler—Riker.

11.30 p.m. Not sleepy. No perspiration. Quite warm at times. Still considerable discharge but very watery especially when I bend my head. Eyes feel heavy and sinuses below are aching dully. A strange thing is that my nose runs and I am unaware of it until I feel it on skin near my lip. Everything about this business is strange. Think I have some feeling and am certainly not depressed.

3rd Phase—Following Three Weeks (Days 11–35)

The subject described this period of time as follows:

I call this the stage of "recovery". Friday morning when I awakened I felt alive and alert. At work, this feeling of well-being became stronger and my emotions seemed to awaken. By noon time I was talking easily with people, joking and laughing. I felt quite happy that I could feel again. During the next several days I felt completely exhausted. The slightest exertion caused an increase in pulse rate, shortness of breath and tightness of chest, feeling of weakness and shakiness. There was no perspiration accompanying this. My eyes and mucous membranes were still dry. This continued for the next 3–4 days then the muscles of my neck and shoulders ached for a few days.

I began to read novels again with interest and also to enjoy TV and music.

During the next week, at times I felt chilly, but usually within an hour I warmed up without medication. When I felt cold my pupils were small but when warm, they dilated to about 1/3. Toward the end of the week, these episodes were less frequent.

My mood was good throughout but I did experience annoyance appropriately. I felt I could not yet empathize normally, but could at least do lip service. I did not experience any other emotion, nor did I worry when this was indicated.

I slept well and felt alert during the daytime. My appetite did not return but as my salivary glands started to function normally once more I had less difficulty in eating.

The second week of this phase found my mucous membranes all right except for my eyes. Outside in the cold there was some slight watering, but other than that they were very dry and ached easily. I gradually resumed my normal interests, showed initiative again and my thinking cleared up totally.

Further excerpts from the daily notes are given.

Eleventh day. 12.0 noon. Returned from work and have made my lunch. Felt increasingly good this a.m. Could relate quite well with people. Talked with G. for about five minutes and joked and laughed with him. I felt almost hot when talking with G. and my palms were wet. Nose running again—no discharge while I was out in the cold.

1.30 p.m. Feel chilly, not real cold. Methedrine 10 mg.

1.40 p.m. Pulse 80.

2.10 p.m. Still chilly.

2.40 p.m. Still chilly. Pupils 1/4. Much less nasal discharge—when I'm cold it lessens and vice versa. Pulse 72.

3.55 p.m. Warmed up immediately after last note and slept until 5 minutes ago. Am comfortable now. Pupils 1/6.

5.30 p.m. Cleaned up and ready to go to H. for dinner. Talked with R. and L. on the phone quite easily. Pupils 1/3. Warm.

6.30 p.m. At H. After about 20 minutes felt chilly. Methedrine 10 mg. Talked easily, laughed and joked. About 7.20 p.m. felt very warm. As time went on felt some strain at carrying on conversation. Didn't have an appetite but ate a good dinner. Felt coolish off and on and quite tired by the time I left about 8.30 p.m. Mood good.

9.0 p.m. Warm and happy.

Twelfth Day (24 January, 1959). 12.45 a.m. I think I'm trying to fight off sleep so I can enjoy this renewed sensation of living. Have been quite warm all evening since I came home. Very little nasal discharge. Skin still very dry. Have rubbed buckets of lotion into it in the last few days. What a wonderful sensation it is to feel again! I've been overwhelmed by my emotions all evening. My question is now—can I feel sorrow? Maybe I'll find out at the play tomorrow night.

1.30 a.m. Have been reading Shaw's letters. Not very interesting. Did this to prevent thinking and feeling my emotions. Am very tired but not sleepy; however, I shall turn out the light now and try to sleep.

4.25 a.m. Light sleep until 4 a.m. when I wakened with the extreme restlessness I had once before. Tossing all over bed. This time I was very hot and heart pounding. Got up now and took Seconal 100 mg. and a glass of milk. Pupils pin point.

5.0 a.m. Turned off light and went to sleep shortly after.

1.40 p.m. Have been working on a business letter and find this quite a stress. I feel cold and my chest feels tight. Pupils are 1/3. Pulse 70. Methedrine 10 mg. and lunch and a break from the letter.

2.05 p.m. Starting to warm up now. Pulse 80.

5.30 p.m. Have been all afternoon writing the one letter. Remained warm—no difficulty in thinking. Affect appropriate. Very little nasal discharge, instead, mucous membranes very dry again.

6.05 p.m. Methedrine 10 mg. Starting to feel chilly. Were I not going out tonight I would try to wait it out (delay taking the methedrine) but at the moment I don't feel up to watching a play. Pupils 1/6. Pulse 68. I feel all used up emotionally after writing the letter, as well as very tired.

6.40 p.m. No change noted as yet. Have been reading the paper but have not absorbed what I read—not like before when I couldn't comprehend and had to keep going back over it —as though I have not the energy really to read and understand. Do I feel a bit low? Perhaps —to me it is being very tired, but that might be a camouflage. Pupils 1/6–1/4, pulse 76. My nose is bothering me terribly—it is so dry. One extreme to the other.

6.50 p.m. Suddenly I'm warm again.

7.15 p.m. Still I feel absolutely beat. Phoned R. to cancel tonight's arrangements. Haven't the energy to get dressed. let alone watch a highly emotional play. Eating supper was a terrific chore—I had to stuff down each mouthful of the meat pie.

8.20 p.m. Still exhausted. Feel as though there is pressure in left epigastric area that causes me to force my breathing. Pupils 1/4. Pulse 80. Nose still bothering me—extremely dry.

9.20 p.m. Breathing less of an effort now. Don't feel quite so tired. I really can't see any depressive feelings—just used up too much adrenaline writing letter, I guess.

10.0 p.m. Am rather passively enjoying the Perry Como show—first enjoyment I have received from TV during this siege. I note any physical exertion, even walking to and from the kitchen causes a sudden surge of heat in my body and a feeling of weakness.

1.40 a.m. Tuinal 200 mg. Feel badly about being such a chicken to take the Tuinal but don't look forward to such a night as last night. Feel I can't cope with this sudden surge of emotions adequately. Guess I'm afraid I may become terribly depressed and may do something impulsively. Am now in bed and will try to read.

Thirteenth Day. Just remembered I had a very beautiful dream last night—in colour—the colour did not make it beautiful, it was the emotional content.

2.55 p.m. What a difference watching the golf today on TV and last Sunday. I sure had no trouble following it, knowing the number of strokes, etc. I became highly involved (rather resented having to make notes through it) so much so that when T. missed the tying putt at the end I jumped right up on the chesterfield involuntarily.

4.0 p.m. Have washed my hair and had a bath. Great exertion. Feeling of tightness across diaphragm. Shaky. Breathing heavily. General feeling of weakness. Pupils 1/3. Pulse 106 after resting for 5 minutes.

4.05 p.m. Pulse 102. Tightness still present. Not as shaky now.

4.15 p.m. Feeling better now. The main thing differentiating this from an ordinary extreme weakness is the lack of perspiration. Pulse 102.

5.15 p.m. Tightness gone. Pulse 82. Have just been resting the past hour and feel quite O.K. now. Pupils 1/4.

6.0 p.m. Least bit of exertion causes a feeling of weakness. Am washing out some lingerie and I have to keep resting while I soak it. Nose very dry now and causing some discomfort.

Fourteenth Day. Turned out light at 12.40 a.m. Had a rotten night's sleep. Seems to me it was hours before I began dozing. Thought of taking seconal but was quite content to lie there even if I didn't sleep at all. When I did sleep it seemed like just dozing to me.

7.45 a.m. At the moment, I do not feel at all rested and it has taken me half an hour to even get started. Feel quite warm. Had several unspectacular dreams.

9.10 a.m. At work. Feel weak. Out of puff and very warm from exertion of coming to work.

9.45 a.m. Feeling of weakness has passed away now. Am doing my regular work with interest. No difficulty in thinking.

10.0 a.m. Starting to feel chilly. Notice now I am first aware of this feeling in the lower parts of my body, rather than hands and arms first, as previously noted.

11.40 a.m. Noticed while walking down corridor a peculiar sensation about my eyes—feel my pupils should be widely dilated—sort of a film before my eyes—pupils are between 1/4–1/6.

12.25 p.m. At home, eyes O.K. now but they feel tired. Muscles across shoulders are aching badly. Mucous membranes of nose dryer than at any other time today.

Fifteenth Day. 7.30 a.m. Up—still sleepy and groggy.

8.15 a.m. Having breakfast now. More alert. Nicely warm. Pupils pin point. Mood seems to be good. Yawning a lot (normal for me in a.m.) which I don't remember doing during these past two weeks. I find real pleasure in yawning and stretching now. It is amazing what simple things give pleasure after such an experience.

8.30 p.m. Pupils 1/4.

1.30 p.m. Back to work after lunch. I have always been sensitive to brilliant sunshine but today the sun at noon caused actual pain in my eyes—they did not water at all—even the sun hitting my peripheral vision caused pain. Wore sun glasses back to work with considerable relief. Did some chores at noon without exhaustion.

2.0 p.m. I read about six pages of handwriting on a chart and my eyes feel very strained—almost to the point of causing vague dizziness—a pulling sensation. Mucous membrane of nose causing little or no discomfort today. Thinking and activity normal tempo.

Sixteenth Day. 7.30 a.m. Had difficulty getting to sleep—eyes so dry I couldn't keep them closed, more comfortable slightly open. Thought I had extreme restlessness with some panic about 5.15 a.m. but this may have been a nightmare—I'm no longer sure. Feel tired and sleepy this a.m.—hard to waken and get going. Quite warm. Nose a bit stuffed up. Pupils 1/6–1/4.

9.40 a.m. Have been at work since 9.0 a.m. No fatigue. Warm. Spirits good. Alert and interested. Pupils 1/6. Forgot to note last night my sense of smell was hyperacute. Lying in bed, trying to sleep, was very sensitive to the smell of my table lighter beside the bed. This has occurred once or twice before in the last week as well.

As of yesterday the outside temperature was −35° F. and my eyes still did not water, nose very slightly runny outside. When I returned from lunch today −31° F. with bright sunlight a tear formed and fell from right eye. Left eye remained dry.

Twenty-First Day. 9.30 a.m. At work—mood good, no sedative hangover. Realize today my emotional tone is still not normal for me. Have felt happy and even irritable (appropriately) but never sad nor anxious even though warranted. My feeling of empathy is still practically totally lacking. I can identify feelings around me but cannot experience these feelings in the situation. Right eye has slight bit of moisture but left eye has none.

Evening—eyes unchanged. Remembered that during the week-end I still did not have my normal response to the music which I usually like. Found myself reading instead of listening to a band I like on T.V. Even when a bongo drummer came on I neither watched nor listened. I was aware of it, but no response. Still have no appetite—eat mechanically at meal time.

Twenty-third Day. Not sad nor anxious—unable to worry. Can use the terms to express these other emotions, e.g. I'm sorry—but this is really lip service. Nose has been quite normal for past three days since Monday a.m.

Twenty-ninth Day. My eyes ached very badly all evening, interfered with reading and to a lesser degree watching TV When I went to bed again, as some time ago, I couldn't close my eyes properly to sleep—as well there was a dull ache in area of antrums above eyes. At 12.30 a.m. decided if I weren't asleep by 1.0 a.m. would take sedation. At 1.0 a.m. decided to wait until 1.30 a.m.—during this time fell asleep as far as I know with eyes slightly open. A.m.—to work—feel refreshed. Mood good. Eyes dry.

Thirty-first Day. Amount of moisture in eyes still not normal. Occasionally when smoke gets in them or I laugh excessively I can feel moisture—otherwise no. Eyes still tired in evenings. Mood has remained on the whole, very good. Yesterday I worked hard all afternoon and evening cleaning house, polishing, doing a washing and all the dishes. Was not tired at all and interest remained high throughout. This is a first since January 10th!

Fourth Phase—Residual Effects Two Months Later

At this time I still have not experienced any feeling of sadness, anxiety or worry. Events have occurred during this period which normally would have resulted in one of these feelings. My ability to empathize has improved but is not present to the same degree as previously.

I sleep well and eat adequately although only rarely have I felt hungry. I seldom feel tired and have my normal energy. My interest is high in my work and at home.

My eyes still bother me and remain very dry except in a cold wind. They ache quite frequently and I find I am unable to read as much as I could before.

I find I feel chilly in the evenings, and keep the thermostat set higher in my house than I ever did before. In the daytime I'm usually quite warm.

The after-effects of this experience compared with my two former experiences with LSD-25 were quite striking. The first time I took LSD-25 was in 1954 and I remember it very vividly. It was largely a perceptual experience and I reacted strongly to all stimuli. The second time I took LSD-25 was one year ago. This time it resembled a transcendental experience and again remains very vivid in my memory. The visual distortions were of a minor nature, but the emotional charge was great. This last time the whole experience seems as though it had happened to someone else. When I concentrate on it I can recall the striking imagery but it has no impact on me even yet. It is easier to recall the total lack of of emotion, but again this is still unreal to me. I can distinctly recall the Saturday morning when I felt I was almost dead, but this seems to have been someone else lying in bed dying—not me. It is very hard for me to realize that those two or three weeks happened in my life and as time goes on it is developing a dream-like quality. On the other hand, it is still very real to my close friends, who tried to relate to me in this strange state.*

* The subject was seen on several occasions by a couple who had known her for ten years (Dr. D. G. McKerracher, Professor of Psychiatry, University of Saskatchewan, and Mrs. McKerracher, a former Psychiatric Nurse). They report as follows:

"On the first night her telephone conversation appeared unaccustomedly formal and stilted.

"On the third night at supper with our family, she was ill at ease, uncomfortable and quite uncommunicative. Later she complained of being chilly, although the room was quite warm. She discussed her experience impersonally and without emotion. She spoke of her lack of feeling and inability to relate to people as if discussing the condition of someone else. She was so detached that we questioned her ability to drive home alone.

"On the sixth day she again visited us. There had been no change from her stilted, formal, rigid manner of three days before. Her conduct now seemed more noticeable, more bizarre, possibly because more people were present. All were amazed and disturbed at her behaviour. When informed that a member of our family had been injured, she showed no evidence of concern.

"During the next week, contacts were by phone. There was no evidence of change; she continued to complain of coldness and dryness of the eyes. She expressed no anxiety about her symptoms, these being described as if they were those of another.

"On the eleventh day, she was next seen. At that time her manner was quite different—she was moderately spontaneous, friendly and accessible."

Five Months Later

My spirits have remained quite high. I can feel happiness and anger appropriately. On the other hand, I have not yet experienced sadness, nor have I worried when the situation warranted concern. I seem to have an abundant amount of energy. I am always more energetic in the spring than at any other time of the year, but this year it seems different. I have worked in the garden until my muscles ached but still enjoyed the work and have not felt fatigued at the end of the day. Perhaps this accounts in part for my greater interest in recreational activities this year as compared with the last few years.

My ability to empathize emotionally has not been normal since the experience. It depends upon the situation. I am able to empathize to some degree with someone who is happy although the experience is for me qualitatively different and is more superficial. However, I can only be aware intellectually of others' sadness or depression. There is no equivalent feeling in myself for the other person.

My eyes are normally moist but still tire fairly easily. In the evenings I find I have to hold books, etc., farther from me to read with ease. It is practically impossible for me to thread a needle at night, whereas I used to be able to do this quite easily.

Rarely have I felt hungry. I usually consume an adequate diet but without any real enjoyment. I have lost seven pounds of excess weight. I sleep well.

I can recall the entire period but it still seems as though it happened to someone else and that I was merely an observer.

Sequence of Recovery

The subject did not recover uniformly in all areas of thought, mood, activity and automatic reactivity. Thinking was not normal by the second day and power to concentrate was defective at day four. The subject remained indecisive about two weeks nor did she trust her memory. Medical instructions about taking methedrine and sleeping sedatives were all written on paper for her. She kept careful notes with times because she was instructed to do so. Visual perception became normal by day four. At this time drapes lost their three-dimensional quality and looked like drapery rather than tapestry. Emotion began to return on day eleven. During this interval, there were periods of feeling only after taking methedrine. The autonomic nervous system was not normal by day fourteen.

Discussion of Biochemical Factors

1. *Response to Sympathomimetic Amines*

Dexedrine given three times did not alleviate the cold feeling although it did make it easier to talk and decreased the discomfort slightly. Methedrine given alone fifteen times in every case but one caused a feeling of warmth which ranged from mild to very hot. Her pupils opened to one-third or better, colour came back to her face and she was able to feel some stirring of emotion. Toward the end of the two week period less methedrine was required to maintain comfort. Thus day eleven required 30 mg./day, twelve 20 mg. and day thirteen and fourteen 10 mg. each.

Methedrine which resembles adrenaline slightly more than does dexedrine was much more effective in alleviating the cold feeling.

The ascorbic acid prevented methedrine from producing its usual autonomic reaction. Beyer (3) showed that ascorbic acid destroys amphetamine *in vitro*. This may account for the lack of response to the methedrine in the presence of ascorbic acid.

There was little or no response to the inhaled adrenaline on the morning of the tenth day. But later the same day an identical dose produced a typical increase in pulse rate, etc. The second inhalation in the morning initiated a copious secretion of mucous fluids which started one hour after and lasted about thirty-six hours. Before and following there was practically no secretion.

Adrenaline and other sympathomimetic amines tend to decrease nasal secretions. The reaction reported here is thus paradoxical. However, adrenaline is the neurohormone transmitter for sweat and perhaps other glands. Therefore they may have ceased to function due to an absence of adequate quantities of adrenaline which was restored momentarily by the inhaled medication.

TABLE I

Reaction to Sympathomimetic Amines

Day	Time	Total Amine (mg.)	Medication	Response
3	1.30 p.m.	25	1. Dexedrine, 10 mg.	Decreased tension, speech easier, some vasodilatation.
	6.00		2. Dexedrine, 15 mg.	No warmth but felt good, speech easier.
4	3.00 p.m.	10	1. Dexedrine, 10 mg.	Not warm, speech easier.
5	9.00 a.m.	15	1. Ascorbic acid, 1 gram	
	2.30 p.m.		2. Methedrine, 5 mg. 3. Ascorbic acid, 1 gram	Very warm, comfortable flush.
	6.00		4. Methedrine, 10 mg.	Very hot, perspiration, flush.
6	1.40 p.m.	20	1. Methedrine, 5 mg.	Warm and flushed after each medication.
	4.35		2. Methedrine. 5 mg.	
	8.30		3. Methedrine, 10 mg.	
7	11.00 a.m.	20	1. Methedrine, 10 mg. and ascorbic acid, 1 gram	Sluggish reaction, no flush.
	2.35 p.m.		2. Methedrine, 10 mg.	No reaction.
	6.00		3. Ascorbic acid, 1 gram	
8	10.30 a.m.	25	1. Ascorbic acid, 1 gram	
	1.55 p.m.		2. Methedrine, 5 mg. and ascorbic acid, 1 gram	No response.
	3.20		3. Methedrine, 10 mg.	No response.
	5.45		4. Methedrine, 10 mg.	No response.
9	10.45 a.m.	30	1. Methedrine, 10 mg. and ascorbic acid, 1 gram	No response.
	1.00 p.m.		2. Methedrine, 10 mg.	Very warm.
	6.00		3. Methedrine, 10 mg.	Warm.
10	8.15 a.m.	40	1. Methedrine, 10 mg.	Warm.
	10.35		2. Methedrine, 10 mg. Adrenaline, 400 μg.	No response.
	11.00		3. 200 μg. adrenaline	Faint flush momentarily.
	2.00 p.m.		4. 200 μg. adrenaline	Immediate reaction and warm.
	3.00		5. Methedrine, 10 mg.	Warm.
	6.00		6. Methedrine, 10 mg.	Warm.

11	8.00 a.m. 1.30 p.m. 6.30	30	1. Methedrine, 10 mg. 2. Methedrine, 10 mg. 3. Methedrine, 10 mg.	Warmed up after each medication.
12	1.40 p.m. 6.05	20	1. Methedrine, 10 mg. 2. Methedrine, 10 mg.	Warm after each medication.
13	1.15 p.m.	10	1. Methedrine, 10 mg.	Warm most of day.
14	10.10 a.m.	10	1. Methedrine, 10 mg.	Warm, flush.

TABLE II

Response to Sympathomimetic Amines

Sympathomimetic Amine	N	Response
Dexedrine	3	In each case speech easier but did not warm up.
Methedrine	15	In each case but one warmed up, flushed, pupils became dilated and became aware of some tingling of emotion.
Methedrine and ascorbic acid together	3	One reaction was sluggish and twice did not react.
Methedrine given within five hours after ascorbic acid	6	There was no reaction three times.
Adrenaline (200 μg.)	1	No response.
	1	No response.
	1	Marked secretion of serous material.

A summary is given from the observer's report of day ten when she was given adrenaline. At 8.15 a.m. 10 mg. methedrine. Pupils pin-point. Warm. Took 10 mg. methedrine at 10.35. Thinking is fair. At 10.50 inhaled 200 μg. adrenaline. At 11.00 inhaled 200 μg. adrenaline. Nothing noted on inhalation. At 11.05 slightly warm for about ten minutes. Cold at 11.25. At 12.30 p.m. marked nasal mucous serous discharge occurred. Subject had felt fairly well except for dry tissues and chilly feeling. She compared this serous discharge with a heavy cold. At 2.03 given 200 μg. adrenaline. In contrast to this morning there was an immediate reaction of pounding heart. Was warm by 2.13 and very warm by 3.00 but without any perspiration. At 3.00 took 10 mg. methedrine. At 6.00 10 mg. methedrine and remained warm. 8.00 felt miserable and sick but not depressed. Became convinced the copious nasal discharge was due to a cold. 11.35, 200 mg. Tuinal.

2. *Paradoxical Reaction to Sedatives*

The day of the experiment no sleep followed 400 mg. of Tuinal and four ounces of rum (60 proof), even though the subject was tired, quiet and apathetic. A further 200 mg. produced sleep only after two and one half hours.

3. *Unusual Reaction to Nicotinic Acid*

This subject has on frequent occasions experimentally taken 1 grəm nicotinic acid and has a predictable vasodilator response. The flush occurs within 20 to 30 minutes and lasts up to one hour. LSD-25 alone does not alter the sequence of reaction, Hoffer (12). This time the nicotinic acid was taken at 1.27 p.m. and the subject was still flushed at 6.00 or four and one half hours later. In spite of the flush when subjects always feel very hot, this subject felt cold.

4. *Secretion of Urine*

LSD-25 is anti-diuretic for the first part of any experience (17). This is then followed by a period of increased diuresis during the latter half of the experience. In this instance the urinary output was markedly decreased throughout the entire first day.

5. *Hypothesis*

The unusual reactions may be accounted for on the assumption that the combination of penicillamine and LSD-25 produced a central and peripheral depletion of sympathomimetic amines. Penicillamine *in vitro* quickly alters adrenochrome to leuco-adrenochrome and possibly prevents an increase of adrenochrome in plasma. LSD-25 increases the secretion of adrenaline (20). Thus the combined effect of increased secretion and rapid consumption of adrenochrome could rapidly deplete the central stores of adrenaline and noradrenaline. If adrenochrome increased in the plasma, it could by a mass action effect slow the secretion of adrenaline.

Reserpine lowers amine concentration in the hypothalamus, in the adrenal gland, Holzbauer and Vogt (15) and in the fibres and ganglia of adrenergic neurones, Muscholl and Vogt (21). When the loss of noradrenaline is severe, there is no response to stimulation. There is also a decrease in arterial walls, Burn and Rand (5). Serotonin is also lowered, Pletscher, Shore and Brodie (25), but the specific effect of inactivating is more likely due to depletion of the amines. Thus only noradrenaline and adrenaline or its precursors as well as amine oxidase inhibitors reverse the reserpine effect, Carlsson, Lindquist, Magnussen and Waldeck (6), Olds and Olds (22). Everett and Toman (8) concluded depletion of serotonin does not play an important role in the behavioural deficit resulting from the active Rauwolfia compounds. John, Wenzel and Tschirgi (16) tested the ability of serotonin, marsilid, adrenaline and noradrenaline to attenuate the effects of reserpine on conditioned behaviour. Of these only adrenaline was active. Methedrine completely reversed the effect of reserpine peripherally.

Thus, it is likely the unusual autonomic response of this subject was due to a depletion of amines both peripherally and centrally. The peripheral lack of amine would account for the vasoconstriction and lack of secretion. Central depletion might account for the internal coldness, pin-point pupils and lack of emotion.

Evidence which favours this suggestion is:

(*a*) Paradoxical autonomic reactions.

(*b*) Remarkable response to adrenaline.

(*c*) Reversal of autonomic reactions by methedrine which was more effective than by dexedrine. This resembles the reversal of the reserpine effect in animals by methedrine and of reserpine induced depressions in humans, Ayd (1).

(*d*) Required two weeks to become reasonably normal. This is the time required in animals to regain normal amine levels in the brain.

(*e*) Ascorbic acid which *in vitro* destroys methedrine prevented it from acting.

(*f*) Sedatives are potentiated by adrenaline. Lack of adrenaline would account for the need for a large quantity of Tuinal the first day and nightly sedation for two weeks (200 to 600 mg. each night).

No one doubts the relationship of adrenaline to anxiety. Usually it is believed too much adrenaline relates to too much anxiety. If true, it is theoretically possible to have too little adrenaline and this could be associated to too little anxiety, i.e. to disinterest, apathy, and, as we have suggested here, to loss of affect.

Discussion of Psychological Response

The most striking feature of the experience was the absence of feeling which followed the LSD-25 experience. As a result the subject found herself (1) unable to relate adequately to others, (2) unable to use affect-laden words, (3) unable to respond to the emotional tempo of a group situation, (4) completely without drive.

Inability to Relate to Others

The inability of schizophrenic patients to relate to others has been described for many years. Various explanations have been offered for this depending upon the orientation of the author. The inadequacy of the subject's reaction is remarkably like the double-bind situation described by Bateson, Jackson, Haley and Weakland (2). In the double bind the schizophrenic patient has been the victim of conflicting demands upon him, one direct and the other abstract. Not knowing to which signal he may respond he becomes ill. These authors suggest that the schizophrenic patient's illness results from such a situation. The schizophrenic exhibits weakness in assigning the correct communication code to stimuli and messages. However, Bateson *et al.* do not consider the possibility that this basic fault may be within the illness and not be a result of faulty transmission .The error may be a faulty receiver. It is difficult to understand why a schizophrenic person should be so perceptive of mother's faulty signals and be so unaware of his own.

However in this subject there has never been any question of schizophrenia so that the basic difficulty in receiving and acting upon stimuli was normal until the experiment. For the next week at least the subject was unable to relate to other people in a normal way. The reason did not lie with the other people. The subject was without affect and simply could not react appropriately to the mood of the other person. Since no emotional participation was possible, there was no way of interacting except by intellectualizing. Conversation is a two-directional process where emotional cues provide the markers; when these are gone, there can be no interaction, merely a series of two-way statements.

The subject reported "one of my colleagues was returning to work for the first time after being awarded his Ph.D. I knew plans were afoot for a royal reception and that there would be a lot of horse-play. I felt doubtful of my capacity to put on an act which would remotely resemble my normal response to such a situation. I knew I could not in any sense be a part of the group, and that I would be overwhelmed and become very confused, so I did not go to work at all that morning. In the afternoon when I met him at work I said something to the effect that I would not congratulate him until I had some feeling."

A large group of words which have emotional meaning such as "thank you", etc. were no longer used by her since they had no meaning. On one occasion, the subject was offered a special box of matches. She realized that to accept she would be expected to thank the giver and found herself unable to do this. Instead she stated "I have a lighter". It is difficult to conceive of the

importance of affect in the use of words. But this experience was a striking demonstration that without emotion many words lose all value.

It was especially difficult to relate to groups. Several days after the experiment, it was possible for her to get along with one person, especially after taking methedrine. However, at this time group interaction was impossible and also dreaded. Coffee breaks are usually group sessions. The subject found these especially difficult. She could remember how she had reacted to similar situations and could sense the mood of the group as a whole. However, she felt it necessary to assess deliberately the mood of each group member in order to relate, so that groups larger than two confused her.

It is not difficult to understand how a loss or distortion of affect can produce a double-bind situation because the affective cues will be missed, distorted or not reacted to. If the ability to have emotion slips away gradually as the disease schizophrenia comes on, the patient loses all reference to an earlier period when reaction to emotion was normal. If the disease comes early in life, no such stable base has existed. Thus, loss of affect in itself can account for many manifestations of schizophrenia. Of course, schizophrenic patients do sometimes have schizophrenic mothers who might experience similar affective difficulties. The double-blind phenomena is according to our point of view a description of a situation which may be caused by a defect in the experiencing of affect.

A Comparison of the Experience and Schizophrenia

Since Bleuler arbitrarily divided schizophrenic symptoms into two classes, changes in thought and affect have been considered primary and changes in gross perception, i.e. hallucinations, secondary. We do not agree that perceptual changes are secondary. There are no studies which prove which symptoms are primary in terms of onset, of importance for diagnosis or for treatment. It may be that distortion of perception destroys the usefulness of environmental cues and so destroys affect. Nevertheless, those who deny the utility of model psychosis experiments do so on these grounds. The experience described here was marked chiefly by a disorder of affect and to a lesser degree of thought.

Plant hallucinogens given alone do not deprive volunteers of affect although it is altered. This experience is the first one we know where LSD-25 so weakened affect that the subject denied its presence for nearly two weeks. However, we have seen somewhat similar reductions of affect in experiments with adrenolutin. In at least six experiments the adrenolutin produced an alteration in affect for up to two weeks duration. One of the first occurred in Dr. H. Osmond. At that time this experience appeared to be a depression. Now in reading the account (nearly five years later), it seems likely affect was lacking rather than being depressed.

The following notes are taken from Dr. Osmond's personal records at the time of the experiment.

On 2 November, 1954, H.O. was given 5 mg. adrenolutin by mouth at 6.20 p.m.

8.10 p.m. An inclination to sink quietly into myself and do just nothing, not even write, but once I start something I can keep going. It is very difficult to speak spontaneously, much easier just to sit. In spite of this I ate a good meal and took part in the conversation but it required some effort.

8.30 p.m. A flatness and great reluctance to do anything, even to think. I feel very remote. I do not have any spontaneity.

8.45 p.m. Very difficult to talk and not very easy to write.

9.0 p.m. It is so hard to realize that this is an important experiment and that a few hours ago I was keenly interested to know the results. Now I know, but it doesn't feel like knowing.

It is intellectually interesting but almost nothing else. No pleasure. No delight as there was this morning. Cut off in some curious way very hard to say.

9.10 p.m. Would like to say how interesting this is, but can muster so little interest inside me that it seems almost hypocritical to say so.

9.40 p.m. Feel a bit livelier, hardly very congenial but alert to carry on a conversation but if I talk I have no inclination to write and vice versa. Tired without being sleepy.

10.25 p.m. Feel very different now, quite alert to take part in conversation and am really thawing out and beginning to take some interest in what has happened. Taking a lively interest in the U.S. election results. It is good to be this way again.

The next day after having slept well, he wrote:

9.15 a.m. Feel flat still but cheered. Inclined to think some residue of this stuff's effect remains but would be hard to lay my finger on it.

3.30 p.m. Don't feel completely myself yet but don't know how to describe this accurately.

7.30 p.m. Have come to the conclusion that this stuff still works. This afternoon I completely forgot the hospital bazaar and was not aware that it was going on. I have never forgotten one before. I was detached from things. Tonight I feel slack and tired.

On 16 December, 1954, Dr. Osmond was given 16 mg. of adrenolutin by mouth. He reported the usual subtle changes in perception, corridors seemed extraordinarily long, voices were remote. In two hours he was peculiarly different. He was remarkably disinterested in matters that would normally have excited him. He appeared to have lost his emotional ability and seemed to be working on a flat, monotonous level. He was very quiet and preoccupied. In four hours he reported he was feeling a great deal livelier and more interested.

For the next two weeks he felt markedly different but did not report this to the senior author. Meanwhile A.H. had taken 16 mg. of adrenolutin by mouth. He continued to react and on the third day became aware of severe depression which lasted throughout the fourth day. He informed H.O. of this experience on 29 December, 1954 when he recovered. H.O. was then reasonably well but began to feel much better because these two independent and unexpected events tended to corroborate each other. It seemed likely his own prolonged reaction was due to the adrenolutin. On 26 December, 1954 he recorded in his notes:

In church I was aware of what seemed like transient fluctuations in the lighting and have noticed this last week a slight frontal headache, lethargy, some thirst with a dry mouth, a sense of detachment without it being quite unreality. I keep wondering whether this has any relationship with adrenolutin or whether it is just fed-upness with Weyburn, the hospital and the prairies where we have now been for several Christmases. Or is it just suggestion? I have always been inclined to putting things by but feel that I have done this more for the past ten days . . . I don't think I would care to be as I have been very long. It is a bloodless sort of existence.

On 28 December, he wrote:

This lethargy is foul. It hangs over one like a smoke cloud. You can't put a finger on it. It means that what one can usually do without effort now requires effort. The pleasantest thing is to let things slide. Let anything slide. Now this could simply mean that I am detaching myself from Weyburn.

On 29 December, 1954, H.O. wrote to A.H.:

And now my old zest and pleasure in life is back. Something that one never misses till it is gone. Yet how hard to be deprived of it. How abysmal to remind oneself that this or that is important because you don't *feel* that it is important but only know it intellectually. Lord Balfour's "nothing matters much and very little matters at all" may be true but it means a zestless life. Monochromatic. It will be interesting to see whether adrenolutin has had anything to do with this or whether it has just been a coincidence that I took some virus infection which began to show itself shortly after the adrenolutin. We must see.

The consequences of a very slowly excreted hallucinogen which could remain circulating and effective in a minor way would fit in well with the known facts of the insidious onset of schizophrenia. For weeks on end you could never quite put your finger on it. Was that vaguely

unpleasant feeling in the head really a headache or "just imagination" or an incipient cerebral tumour . . . In this hypochrondriacal state one finds some comfort in making one's diffuse and intangible discomforts concrete. Yet can this stuff possibly have acted for fourteen days. It seems improbable but is not completely impossible. Though I would suspect that it is a cold or something that has complicated things . . . As we talked (to A.H. by long distance telephone) I felt my *joie de vivre* returning. Something that had not been possible except for fleeting intervals for fourteen days is now back and yet though it makes a vast difference to life I would be hard put to say what had happened. So there you are. I didn't tell you because I was a trifle ashamed when it was past and did not want to suggest anything to you.

Dr. Osmond's prolonged experience in many ways resembled the one which followed penicillamine and LSD-25. We believe this affectless state produced in this subject by penicillamine and LSD-25 and in H.O. by adrenolutin are useful models of natural schizophrenia. If true then it becomes obvious how important is the restoration of affect in the treatment of schizophrenia. Much more attention must be given to the role of affect and to its influence upon thought and thus on behaviour.

Summary

A subject given LSD-25 after two days' treatment with penicillamine developed a psychosis characterized primarily by loss of affect for two weeks. Her two previous reactions to LSD-25 were similar to those described in the literature. We postulate that this combination of chemicals depletes the sympathomimetic amine content of the peripheral and central stores thus producing the disorder of affect as well as of autonomic reversal.

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Drug-Induced Schizophrenia

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